Prenatal antibiotic exposure and the risk of atopic dermatitis in children: a nationwide population-based cohort study.

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Abstract

Background: Atopic dermatitis (AD) contributes to substantial social and financial costs in public health care systems. Antibiotic exposure during pregnancy has been proposed as a risk factor, but findings remain inconsistent. The aim of this study was to investigate the association between prenatal antibiotic use and childhood AD. **Methods:** We performed a population-based cohort study using data collected from the Taiwan Maternal and Child Health Database from 2009 to 2016. Associations were determined using Cox proportional hazards model and were adjusted for several potential covariates, including maternal atopic disorders and gestational infections. Subgroup analyses evaluated the influence of postnatal infant antibiotic/acetaminophen use on the association between prenatal antibiotic exposure and childhood AD diagnosed after 1 year of age. **Results:** A total of 1288343 mother-child pairs were identified and 39.5% received antibiotics prenatally. Maternal antibiotic use during pregnancy was slightly positively associated with childhood AD (aHR 1.05, 95% CI 1.04-1.06), especially in the first and second trimesters. An apparent dose-response pattern was observed with an 11% increased risk when the exposure was [?]5 courses prenatally (aHR 1.11, 95% CI 1.09-1.14). Subgroup analysis showed the positive association remained significant regardless of postnatal antibiotic use; however, a negative association was found in children without postnatal infant acetaminophen use (aHR 1.02, 95% CI 0.97-1.07). **Conclusion:** Maternal antibiotic use during pregnancy was associated with increased risk of childhood AD in a dose-related manner. Possible confounders existed between prenatal antibiotics and postnatal infant acetaminophen use in the subgroup analysis. Further research may be warranted to investigate this variable using a prospectively designed study, and also to examine whether or not this association is specifically related to pregnancy.

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Abstract

Background: Atopic dermatitis (AD) contributes to substantial social and financial costs in public health care systems. Antibiotic exposure during pregnancy has been proposed as a risk factor, but findings remain

inconsistent. The aim of this study was to investigate the association between prenatal antibiotic use and childhood AD.

Methods: We performed a population-based cohort study using data collected from the Taiwan Maternal and Child Health Database from 2009 to 2016. Associations were determined using Cox proportional hazards model and were adjusted for several potential covariates, including maternal atopic disorders and gestational infections. Subgroup analyses evaluated the influence of postnatal infant antibiotic/acetaminophen use on the association between prenatal antibiotic exposure and childhood AD diagnosed after 1 year of age.

Results: A total of 1288343 mother-child pairs were identified and 39.5% received antibiotics prenatally. Maternal antibiotic use during pregnancy was slightly positively associated with childhood AD (aHR 1.05, 95% CI 1.04-1.06), especially in the first and second trimesters. An apparent dose-response pattern was observed with an 11% increased risk when the exposure was [?]5 courses prenatally (aHR 1.11, 95% CI 1.09-1.14). Subgroup analysis showed the positive association remained significant regardless of postnatal antibiotic use; however, a negative association was found in children without postnatal infant acetaminophen use (aHR 1.02, 95% CI 0.97-1.07).

Conclusion: Maternal antibiotic use during pregnancy was associated with increased risk of childhood AD in a dose-related manner. Possible confounders existed between prenatal antibiotics and postnatal infant acetaminophen use in the subgroup analysis. Further research may be warranted to investigate this variable using a prospectively designed study, and also to examine whether or not this association is specifically related to pregnancy.

Key message:

Prenatal antibiotic use was positively associated with atopic dermatitis in childhood in a dose-response manner. Further research should be conducted to examine whether or not this association was specific to during pregnancy.

Introduction

Atopic dermatitis (AD) is an inflammatory skin disorder characterized by recurrent pruritic eczematous lesions. The prevalence of AD varies among different geographic areas, with a rate of up to 20% in the pediatric population.[1] AD manifests mostly in infancy with an age of onset before 6 years in about 80% of patients.[2] Dermatitis, including AD, is responsible for the majority of the global skin disease burden, leading to substantial social and financial costs.[3]

The cause of AD may be multifactorial, including genetic susceptibility, environmental exposure, immune dysregulation, and inflammation.[4,5] Among the environmental variables, antibiotic use during pregnancy and in early life are thought to be risk factors of AD and have been discussed in several studies and meta-analyses. Antibiotics account for nearly 80% of prescribed medications during pregnancy and the estimated rate of antibiotic use during this period was reported to be 20-25%.[6] The changes in gut microbiota and dysbiosis after antibiotic use may be one of the reasons for subsequent AD development.[7]

Tsakok el al. conducted the first systematic review and meta-analysis of the effects of prenatal antibiotic exposure on AD. The pooled odds ratio (OR), which was 1.3 (95% CI: 0.86-1.95), indicated there was no association, although the estimate was elevated.[8]Three subsequent meta-analysis showed a positive association.[9-11] In a study by Cait et al., the risk of eczema/dermatitis was increased in their pooled data (RR 1.28; 95% CI: 1.06 –1.53). However, high heterogeneity among the data was also mentioned by the authors. Similar findings were also noted in the other 2 meta-analyses. The reasons for the high heterogeneity may be the different methods of data collection (some were by questionnaire or telephone interviews), inconsistent outcome measurements, and differences in methods used to control the variables among studies.

This study employed a cohort study design with a large sample from Taiwan's national healthcare system and aimed to examine the association between maternal antibiotic use during pregnancy and childhood AD, taking the timing of exposure during pregnancy into account.

Methods

2.1 Data source

The data used in this study were from the Taiwan Maternal and Child Health Database (TMCHD), which consists of four linked nationwide databases, namely the National Health Insurance Research Database (NHIRD), the Birth Certificate Application (BCA) database, Birth Registration Database (BRD), and the National Register of Death (NRD) in Taiwan.

The NHI (National Health Insurance) program was launched in Taiwan in 1995 and covers over 99% of the nation's population of approximately 23 million residents, with medical claims data on all outpatients and inpatients. Information regarding demographic data, dates of visits, disease diagnoses, prescriptions, and medical orders are included in the NHIRD. Information related to birth of children and nationality of mother are included in the BCA database, whereas the NRD contains the survival status of infants. Using the unique personal identification numbers of residents in Taiwan, we were able to confirm the relationships between parents and children through the BRD and link individuals across the four databases. The diagnosis of diseases was based on the *International Classification of Diseases, 9th* and*10th Revision, Clinical Modification* (*ICD-9-CM* and*ICD-10-CM*). The study was approved by the ethical review board of Chung Shan Medical University Hospital.

2.2 Study population and design

We conducted a retrospective cohort study by analyzing data from children born between 2009 and 2016 from the TMCHD. A total of 1459093 labor events were identified initially. After excluding mothers with foreign nationality (n =88837), stillbirths or miscarriages (n = 14639), and newborns with missing identification numbers (n = 67274), there were 1288343 mother-child pairs (Figure S1). The exposure of antibiotics during pregnancy, as well as the dose and timing, was identified by using Anatomical Therapeutic Chemical Classification (ATC) code J01. The index date was set as the birth date. The trimester in which antibiotic exposure occurred was defined as follows: first, 1-91 days; second, 92-189 days; third, [?]190 days. The outcome variable was defined as outpatient visits at least 3 times or one hospitalization with a diagnosis of atopic dermatitis (ICD-9-CM: 691 or ICD-10-CM: L20) after the index date. Maternal comorbidities were defined as comorbidities occurring two years before the index date and at least 3 outpatient visits or one hospitalization, whereas gestational infections, gestational diabetes, and preeclampsia were defined as at least one outpatient visit or hospitalization. The exposure and non-exposure group were followed up until the onset of atopic dermatitis, death, or 31 December 2019, whichever occurred first.

2.3 Potential confounders or covariates

We considered the following covariates for potential association with exposure and outcome based on previous studies.[2,12]Maternal factors included maternal age, urbanization, insurance property, mode of delivery, type of pregnancy, acetaminophen use during pregnancy, maternal atopic disorders, gestational infections, and maternal comorbidities, including hypertension, diabetes mellitus, hyperlipidemia, malignancy, urinary tract infection, maternal asthma, rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, endometriosis, gestational diabetes, and preeclampsia. Infant factors included birth year, child's sex, length of gestation, birth weight, and APGAR score at birth. In addition, postnatal antibiotic and acetaminophen exposure in the first year of life were also selected as variables based on previous reports.

2.4 Statistical analysis

We used absolute standardized differences (ASD) to measure the effect size of baseline covariates between groups. When the ASD was <0.1, the characteristics between two groups were considered similar. In addition, Kaplan-Meier analysis was used to calculate the cumulative incidence of AD and a log-rank test was used to measure the significance between groups. We used a Cox proportional hazards model to estimate the associations of maternal antibiotic use during pregnancy with childhood AD and associated covariates, which were reported as crude and adjusted hazard ratios (HR and aHR, respectively) and 95% confidence intervals. To consider the effect of infant antibiotic/acetaminophen use on prenatal antibiotic exposure and

avoid reverse causation (AD occurred before antibiotic/acetaminophen use), we performed an analysis with exclusion of AD diagnosed before 1 year of age, as shown in the subgroup analysis. All calculations were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

3.1 Demographic data of the study subjects

A total of 1288343 mother-child pairs were included in our study with a median follow-up time of 61 months, and the mean (SD) age of AD diagnosis was 0.81 ± 1.1 years old. The mean maternal age was 31.38 ± 4.6 years and 508647 (39.5%) received antibiotics during pregnancy. The prevalence of AD in our cohort was 22.3%, corresponding to the incidence rate of 3.69 (95% CI 3.68-3.71) per 1000 person-months. The frequency of maternal antibiotic use varied slightly during pregnancy, from 17.9% in the first trimester to 19.0% in the second and 14.6% in the third trimester.

As shown in Table 1, the infants of mothers exposed to prenatal antibiotics were more likely to be born preterm than infants of unexposed mothers, but there was no association with increased risk of AD (aHR 0.98, 95% CI 0.96-0.99) (Table 3). In contrast, prenatal acetaminophen exposure, gestational infections, and maternal atopic disorders, such as allergic rhinitis, and AD were positively associated with prenatal antibiotic use and AD risk (Table 1, Table 3). The exposure and unexposed groups were similar regarding childbirth year, sex distributions, birth weight, Apgar scores at birth, maternal age, urbanization, insurance properties, mode of delivery, type of pregnancy, and paternal age (Table 1). Infants born to mothers with prenatal antibiotic exposure were more likely to be exposed to postnatal antibiotics and acetaminophen than those born to unexposed mothers in the first year of life (Table 1). We performed a subgroup analysis that only included AD diagnosed after 1 year of age, as shown in Table 5, which still showed a positive association with AD in the prenatal exposure group, but the estimate was attenuated after adjusting for potential covariates and was even reduced to null in children who were not exposed to postnatal acetaminophen (aHR 1.02, 95% CI 0.97-1.07).

3.2 Relationship between prenatal antibiotic exposure and atopic dermatitis

In the present study, prenatal antibiotic exposure was associated with higher rates of AD (4 per 1000 person-months, 95% CI 3.98-4.03) compared to unexposed groups (3.5 per 1000 person-months, 95% CI 3.48-3.52) (HR 1.13, 95% CI 1.12-1.14) (Table 2). After adjusting for covariates, the association still persisted in the Cox proportional hazards model (HR 1.05, 95% CI 1.04-1.06) (Table 2). The cumulative probability of AD was significantly higher in the prenatal antibiotic exposure group than in the non-exposure group (log-rank test $P<0.001$, Figure 1).

3.3 Timing of prenatal antibiotic exposure and AD risk

Regarding the timing of prenatal antibiotic exposure and AD risk, the risk was slightly higher in the first trimester (aHR 1.04, 95% CI 1.03-1.05) and second trimester (aHR 1.03, 95% CI 1.01-1.04) than in the third trimester (aHR 1, 95% CI 0.99-1.01), in which the risk became non-significant. When the reference group was set as "no antibiotic use during the whole pregnancy", the risk of AD was slightly increased in all three trimesters (first trimester: aHR 1.06, 95% CI 1.05-1.08, second trimester: aHR 1.06, 95% CI 1.05-1.07, and third trimester: aHR 1.04, 95% CI 1.02-1.05) (Table 4).

3.4 Cumulative prenatal antibiotic courses and AD risk

We observed a significant dose-response association between number of prenatal antibiotic courses and AD. With a mean of 2.1 courses of antibiotic use during pregnancy, the adjusted HRs were 1.05 (95% CI 1.04-1.06) for 1-2 courses of antibiotic use, 1.08 (95% CI 1.06-1.1) for 3-4 courses of antibiotic use, and 1.11 (95% CI 1.09-1.14) for [?]5 courses of antibiotic use (Table S1).

Discussion

In this population-based study, we found a positive association between prenatal antibiotic exposure in

all trimesters and development of AD in childhood. This association remained significant after adjusting for several established AD risk factors in the hazards model analysis. The positive association remained significant in the subgroup analysis regardless of postnatal antibiotic use after excluding AD diagnosed before 1 year of age, but the association did not persist in children who were not exposed to postnatal acetaminophen. We also found an apparent dose-response relationship with an 11% increased risk when exposed to [?]5 courses prenatally. To our knowledge, this is the largest study to date to investigate the relationship between maternal antibiotic use during pregnancy and offspring AD.

The gut microbiome and the intestinal immune system develop in parallel in the first trimester, which is also when enrichment of innate immune cells in skin takes place.[13,14] Studies have reported that intrauterine samples/placenta harbor bacterial DNA or biomass and its colonization may begin in utero.[7,14-16] However, whether the bacterial DNA are present in the placenta is still a matter of debate, as some studies have suggested the presence of DNA may be caused by contamination during the DNA purification process.[16] Nevertheless, the maternal microbiome can potentially influence fetal immune maturation through agonists of toll-like receptors (TLRs), short-chain fatty acids (SCFAs) or lipopolysaccharides (LPS) via the placenta.[16,17]Proper differentiation, specification and complete development of adaptive immunity rely on the interactions between gastrointestinal-associated lymphoid tissue (GALT) and the gut microbiome.[14] Dysbiosis, which refers to imbalances in gut microflora and changes in their functional composition, local distribution, and metabolic activities,[18] may potentially lead to allergy and atopic diseases.[14,19]Dysbiosis that occurs during the critical time window of immune development, even within a short-term period, may have a long-term impact on immune health.[14]

Comparison with other studies

Our results are consistent with a cross-sectional study by McKeever et al., who used a birth cohort of 24690 children derived from the General Practice Research Database in the United Kingdom, and found a positive association between prenatal antibiotic use and doctor-diagnosed eczema in a dose-related manner.[20] In line with our results, their study also revealed that infections during pregnancy increased the risk of allergic diseases and adjusting for them did not notably affect the estimates. Dom et al. conducted a prospective birth cohort study of 773 children in Belgium. A questionnaire was used to investigate parent-reported eczema, and the results revealed that prenatal antibiotic exposure was strongly positively associated with eczema in children up to 4 years old after adjusting for post-natal antibiotics.[21] Conversely, two Danish cohort studies that used a prospective design were conducted by Stensballe et al. and the results showed that prenatal antibiotic use did not influence the risk of eczema in 411 and 30675 children, respectively.[22] However, their follow-up period was shorter and did not take exposure in all trimesters into account. In addition, a study by Sasaki et al. who used a Japanese nationwide dataset to conduct a prospective birth cohort study showed no association between prenatal antibiotic exposure and diagnosed or observed AD at 1 year old in 70408 children (aOR 1.01, 95% CI 0.97-1.06).[23] Similar to the study by Stensballe et al., their follow-up period was also shorter and excluded children born through cesarean delivery, which may influence the risk of prenatal antibiotic exposure in AD.

A recent prospective cohort study performed by Mubanga et al. investigated 722767 singleton children and 74663 discordant siblings in Sweden. In line with our results, they found the risk of AD was greater in children exposed to prenatal antibiotics than in those who were not exposed (aHR 1.10, 95% CI 1.09-1.12), whereas no such increased risk was found in the sibling-control analysis, suggesting some familial confounders.[24] Based on the covariates they adjusted for, we further adjusted the maternal comorbidities, maternal AD, maternal allergic rhinitis, gestational infections, and maternal acetaminophen use during pregnancy, which may be potential risk factors according to previous studies.[12,25,26] In addition, their study revealed an apparent dose-response relationship, and the category of infection did not modify the association of maternal antibiotic use and child AD, which was consistent with our results. In terms of the trimester-specific association between antibiotic exposure during pregnancy and childhood AD, their results were comparable with our results in that the risk increased in all trimesters; however, our data showed a slightly higher risk in the first and second trimesters compared with the third trimester, which might be explained by antibiotics-related dysbiosis or

immunomodulatory effects, phenomena that are known to have a greater impact during early pregnancy.

Several studies and meta-analyses revealed that post-natal antibiotics and acetaminophen exposure were associated with an increased risk of AD, especially within the first year of life.[27-29] Antibiotics and acetaminophen are frequently used to treat infection. However, reverse causation must be taken into consideration, so we performed a subgroup analysis by independently examining the effects of these two medications on AD. After excluding AD diagnosed before 1 year of age, the positive association was still present in the prenatal antibiotic exposure group regardless of postnatal antibiotic use, but the adjusted hazards reduced to null in children who were not exposed to postnatal acetaminophen, suggesting that some confounders common to both prenatal antibiotics and postnatal acetaminophen use existed (e.g., infection, fever, or AD itself). However, the majority (87%) of AD patients in our cohort were diagnosed before 1 year of age, so this negative association could only represent the minority (13%) of AD patients diagnosed after 1 year of age. Our results are consistent with a study by Dom et al. that found adjusting for post-natal antibiotics did not significantly change the result showing prenatal antibiotic use increased the risk of childhood AD.[21]

Even though our results showed a positive association between maternal use of antibiotics during pregnancy and childhood AD, this does not necessarily imply a causal link between the two. A registry-based cohort study conducted by Stokholm et al. investigated the temporal association between maternal antibiotic use and childhood asthma and showed that the risk of asthma was similar among 80 weeks before pregnancy, during pregnancy, and 80 weeks after pregnancy.[30] The authors suspected that maternal antibiotic use is a surrogate marker of maternal propensity for infection, which is the true cause of childhood asthma. Loewen et al. replicated their results in a retrospective cohort study and proposed that some unmeasured factors, such as healthcare utilization patterns, shared familial factors, and maternal deficiency of vitamin D or other immunomodulatory nutrients may explain both the increased risk of maternal antibiotic use/infection and the increased risk of asthma in offspring.[31] While we could not address the temporal association between maternal antibiotic use before and after pregnancy, our results were unchanged after adjusting for three common infections during pregnancy. Furthermore, maternal antibiotic use may also be a surrogate marker of infant antibiotic use, which is associated with asthma and AD.[31] Our data showed that infants born to mothers who received antibiotics during pregnancy were indeed more likely to be exposed to postnatal antibiotics; however, the positive association between maternal antibiotic use during pregnancy and childhood AD remained significant in the subgroup analysis independent of infant antibiotic use.

Strengths and Limitations

The major strengths of this study were its large sample size, long follow-up period, and its population-based sample, which was representative of Taiwanese residents. The diagnosis of AD in our study was given by board-certified pediatricians or dermatologists, and therefore recall bias and detection bias was likely minimal. In addition, we were able to adjust for some covariates, including gestational infections and maternal acetaminophen use during pregnancy, which were not addressed in previous studies. Our analysis of the effect of prenatal antibiotic exposure on AD diagnosed after 1 year of age and its relationship with infant antibiotic/acetaminophen use may have partly taken confounding by indication (increased infection or fever that led to increases in both AD and antibiotic/acetaminophen exposure) into account in our study, which has not been mentioned previously.

The major limitation of our study is that some covariates, which may influence the risk of AD due to maternal antibiotic use during pregnancy, such as maternal smoking, patients' consulting behavior or healthcare utilization patterns, dietary habits, environment exposures (e.g., climate conditions, air pollution, etc.) and some unmeasured factors shared by families,[2,24,32] were not adjusted for in our analysis. It is also possible that mild cases of AD who did not seek medical help were not identified in our analysis. However, the Taiwan NHI is an easily accessible, low-cost medical insurance system. Finally, we were not able to analyze the effect of prenatal antibiotics on AD by types of antibiotic use, which may have influenced the risk in patients with asthma.[10,11] However, to our knowledge, this effect did not exist when investigating the influence of antibiotic exposure during pregnancy on offspring AD.[9,20,24,33]

In conclusion, this cohort study revealed that maternal antibiotic use during pregnancy was associated with a slightly increased risk of childhood AD. This association was similar among trimesters during pregnancy and an apparent dose-response pattern was observed, although the association may have been partly confounded by postnatal acetaminophen use in AD diagnosed after 1 year of age. Further research should be conducted to investigate this confounder in a prospectively designed study and to explore the timing before or after pregnancy in order to elucidate whether or not this association was specific to during pregnancy. Nevertheless, we believe that antibiotics should be used prudently during pregnancy and that this potential effect should be taken into account.

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